Journal of Affective Disorders 203 (2016) 332–338

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Association between major depressive disorder and odor identification impairment

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ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form
3 June 2016
Accepted 7 June 2016
Available online 8 June 2016

Keywords:
Odor identification impairment
Major depressive disorder
Symptom severity
Disease course severity

ABSTRACT

Background: There is evidence of olfactory deficits in patients with major depressive disorder (MDD) but causes and mechanisms are largely unknown.
Methods: We compared 728 patients with current MDD and 555 non-depressed controls regarding odor identification impairment taking into account the severity of acute symptoms and of the disease course. We assessed current symptom severity with the Hamilton Depression Rating Scale, and disease course severity based on admission diagnosis (ICD-10, F32/F33) and self-reported hospitalization frequency, defined as infrequent (<2) and frequent (≥ 2) depression-related hospitalizations under constant disease duration. A score of <10 on the Sniffin' Sticks-Screen-12 test determined the presence of odor identification impairment.
Results: Compared to non-depressed controls patients with frequent (rapidly recurring) hospitalizations had an elevated chance of odor identification impairment, even after adjustment for smell-influencing factors, such as age and smoking, (OR = 1.7; 95% CI 1.0–2.9). Patients with recurrent MDD (F33) also had an elevated odds of odor identification impairment compared to those with a first-time episode (F32, OR = 1.5; 95% CI 1.0–2.4). In patients with a first-time episode the chance of odor identification impairment increased by 7% with each point increase in the Hamilton Score.
Limitations: Cross-sectional study. Variation in the use of psychotropic medication is a potential bias.
Conclusion: Odor identification impairment was evident in MDD patients with first-time high symptom severity and in patients with a severe disease course. Whether odor identification impairment is a marker or mediator of structural and functional brain changes associated with acute or active MDD requires further investigations in longitudinal studies.

1. Introduction

Major depressive disorder (MDD) ranks as one of the leading causes of disability (Ferrari et al., 2013). The underlying neurobiological model of MDD is yet not satisfactorily determined, however, evidence exists for the involvement of functional, structural, and/or molecular alterations in several areas of the brain (Bhagwagar et al., 2002; Drevets, 1998; Lorenzetti et al., 2009; Maletic et al., 2007). Some of these areas are essential for the processing of olfactory information, for example limbic and prefrontal structures (Eslinger et al., 1982; Martzke et al., 1997; Potter and Butters, 1980; Wilson et al., 2014), and mounting evidence shows pronounced olfactory deficits in patients with MDD, which can be caused by dysfunctions at different stages of the olfactory system (Clepce et al., 2010; Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pause et al., 2001; Pollatos et al., 2007; Schablitzky and Pause, 2014; Zucco and Bollini, 2011). Different olfactory methods can be applied to roughly localize these dysfunctions. A poorer olfactory threshold, for instance, is supposed to rather reflect dysfunctions on a primary processing level, such as the olfactory receptors and/or olfactory bulbs, whereas a reduced ability to identify odors is thought to indicate malfunctions on a higher processing level, such as the frontal areas (Burón and Bulbena, 2013; Martzke et al., 1997; Negoias et al., 2010; Schablitzky and Pause, 2014).

The majority of the few available clinical studies shows evidence for poorer olfactory thresholds in patients with acute MDD

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http://dx.doi.org/10.1016/j.jad.2016.06.022
0165-0327/

compared to non-depressed controls, with a more pronounced impairment in patients with severe symptoms (Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pause et al., 2005, 2001). There is also evidence of an association between depression and parosmia/phantosmia (Croy et al., 2013). In contrast, among the few available studies on odor identification most have reported intact abilities in patients with an acute episode of MDD compared to non-depressed controls (Amsterdam et al., 1987; Croy et al., 2014; Kopala et al., 1994; Lombion-Pouthier et al., 2006; Naudin et al., 2012; Negoias et al., 2010; Swiecicki et al., 2009; Warner et al., 1990), while only three studies have observed impaired odor identification (Clepce et al., 2010; Serby et al., 1990; Zucco and Bollini, 2011).

The inconsistent findings may be explained (at least partly) by differing methods used to assess and define odor identification impairment as well as the different clinical characteristics (symptom severity and severity of the disease course) of the included patients with MDD. For example, Lombion-Pouthier et al. (2006) found no difference between 49 patients with a first diagnosis of severe depression and 58 non-depressed controls. Impairment was diagnosed as identification of less than 16 out of 16 odors. Swiecicki et al. (2009) have reported a similar mean odor identification score (ranging from 0 to 16) between 20 patients with recurrent MDD and 30 controls. In a recent study by Zucco and Bollini (2011), 12 patients with severe symptoms of MDD had a lower mean score of correctly identified odors compared to 12 age and sex matched controls, while further 12 patient with mild symptoms did not differ from controls. MDD severity was defined according to the DSM-IV criteria.

The use of mean scores to compare odor identification performance across groups may not allow for the clinically important differentiation between persons with “normosmic” from “hyposmic” olfaction. Furthermore, the small size of the studies ranging from 14 (Warner et al., 1990) to 107 (Lombion-Pouthier et al., 2006) included individuals does not provide enough statistical power to detect mild or medium-sized associations (Button et al., 2013). Given the heterogeneity of depression with respect to symptom severity, disease course severity (e.g., number of recurrent episodes) and pathophysiology, alterations in olfactory identification performance are possibly specific to certain disease characteristic and may act as a maker for short-term or long-term dysfunctions, or even both. Whereas some of the above mentioned studies on odor identification impairment in MDD examined severity of acute symptoms, the severity of the disease course has been neglected, so far.

The aim of the present study was to examine whether MDD is related to odor identification impairment when compared to non-depressed controls in a large sample of 728 patients and 555 population controls. We further thought to address whether current symptom severity and disease course severity act as short and long-term indicators, respectively, of potential brain changes that differentiate patients with intact from patients with impaired odor identification.

2. Methods

2.1. Study population

The sample for this cross-sectional analysis is based on the BiDirect Study, an ongoing prospective cohort study that examines the pathways between depression and arteriosclerosis in participants aged 35–65 years. For a detailed description of the BiDirect study please see Teismann et al. (2014). Participants were recruited into three different cohorts. Cohort 1 encompassed 999 patients with a current episode of depression at the time of recruitment, cohort 2 included 347 patients with a recent, acute cardiovascular event, and cohort 3 included 912 persons randomly drawn from the general population of the city of Münster. In the present analysis, only baseline data from cohorts 1 and 3 were considered.

The baseline assessment was conducted from July 2010 to June 2013. Patients with depression (cohort 1) were recruited from six psychiatric and psychosomatic hospitals and several practices in the Münster region in North-Western Germany. Inclusion criteria were current in- or out-patient treatment because of an acute episode of depression; patients with comorbid dementia or substance abuse were excluded from study participation. Patients potentially eligible for participation were identified by trained and certified study psychologists. The BiDirect Study was approved by the ethics committee of the University of Münster and the Westphalian Chamber of the Physicians in Münster (Teismann et al., 2014).

For the present analyses, only those patients with depression with an ICD-10 diagnosis of either a first-time episode of MDD (F32) or recurrent MDD (F33) at admission were included (n=922 out of 999). From the population-based controls, individuals with a Center for Epidemiological Studies Depression Scale (CES-D) score (Radloff, 1977) of $\geq$16 and/or a history of a physician diagnosed depression were excluded in order to receive a non-depressed control group (n=170). We further excluded participants with a history or imaging evidence of stroke or multiple sclerosis as well as those with a history of epilepsy, brain tumor or Parkinson's disease (n=72). Another 176 participants, who were not born in German-speaking areas were excluded because studies have reported that odor identification might be sensitive to cross-cultural differences (Sorokowska et al., 2014). Moreover, a total of 14 persons did not participate in the olfactory performance tests. Another 119 participants were excluded because of missing values in any of the explanatory variables. Thus, a total of 1283 datasets were available for the present analyses, including 555 non-depressed controls and 728 patients with MDD.

2.2. Measures

Socio-demographic characteristics, smoking status, and data on the participants' health status and disease history were assessed in a personal interview by trained interviewers. Body mass index (BMI) was calculated from measured weight and height (kg/m^2) and categorized into BMI $< 30\ kg/m^2$ and BMI $\geq 30\ kg/m^2$ (obesity). The CES-D was administered to assess the presence of depressive symptoms in all participants. A cut-off score of $\geq$16 was applied to define clinically relevant depressive symptomatology in control participants (cohort 3).

The interview also included questions on the participants' current medication, which were coded according to the Anatomical Therapeutic Chemical Classification System (ATC). We classified psychotropic medication as the intake of psycholeptics (ATC-N05; including intake of antipsychotics, anxiolytics, hypnotics and sedatives) and/or psychoanaleptics (antidepressants, ATC-N06) at the time of the study examination. For analyses, we categorized the intake of psychotropic medication as “no psychotropic medication”, “intake of psycholeptics”, “intake of psychoanaleptics”, or “intake of psychoanaleptics and psycholeptics”.

2.2.1. Clinical characteristics of MDD

In addition to the personal interview, a structured clinical interview in patients with depression was conducted by trained psychologists. This clinical interview also included the assessment of symptom severity using the 17-items version of the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). The HAM-D total score was divided into the categories: “remitted symptoms